



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

NOV 23 1993

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Chlorpyrifos

OFFICE OF  
PREVENTION, PESTICIDES AND  
TOXIC SUBSTANCES

CASRN. 2921-88-2  
EPA Chem. Code: 059101  
Caswell No. 219AA

FROM:

George Z. Ghali, Ph.D. *G. Ghali 9.14.93*  
Manager, RfD/Quality Assurance Peer Review  
Health Effects Division (H7509C)

TO:

Dennis Edwards, PM 19  
Insecticide-Rodenticide Branch  
Registration Division (H7505C)

The Health Effects Division RfD/Peer Review Committee met on September 9, 1993 to discuss and evaluate the existing toxicology data in support of Chlorpyrifos re-registration and to reassess the Reference Dose (RfD) for this chemical.

The Committee considered the chronic toxicity/carcinogenicity study in rats (83-1a and -2a), the long-term feeding study in dogs (83-1b), the carcinogenicity study in mice (83-2b), the developmental toxicity studies in rats and rabbits (83-3a and -3b) and the reproductive toxicity study in rats (83-4) to be acceptable. The Committee recommended that summary tables of the most frequently observed tumors in both the rat and mouse studies be included in the data evaluation records for these studies.

A Reference Dose (RfD) for chlorpyrifos had been assessed by the Health Effects Division-RfD Committee on February 21, 1986 and verified by the Agency RfD Work Group on March 11, 1986. The RfD based upon a no-observable effect level (NOEL) of 0.03 mg/kg/day for plasma cholinesterase inhibition in human subjects using an Uncertainty Factor (UF) of 10 to account for the intraspecies variability. On this basis, the RfD was calculated to be 0.003 mg/kg/day. In the meeting of September 9, 1993 the Committee recommended that the existing Reference Dose remain unchanged. It should be noted that an RfD value of 0.01 mg/kg/day was established for chlorpyrifos by the WHO in 1982.

The high dose levels tested in the carcinogenicity studies in rats and mice were considered adequate for carcinogenicity testing as demonstrated by the depression of cholinesterase. The chemical did not alter the spontaneous tumor profile in these strains of rats and mice under the testing conditions. The chemical was,



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contains at least 50% recycled fiber

therefore, classified as a "Group E" carcinogen.

Since chlorpyrifos is a potent cholinesterase inhibitor and has the potential to cause other neurotoxic effects, the Committee determined that developmental as well as subchronic neurotoxicity studies should be conducted. The Committee felt that potential ocular effects should also be addressed.

A. Individual in Attendance

1. Peer Review Committee Members and Associates present in at least one of the two meetings (Signature indicates concurrence with the peer review unless otherwise stated).

William Burnam

W. Burnam

Reto Engler

Reto Engler

Marcia Van Gemert

Marcia Van Gemert

Karl Baetcke

Karl Baetcke

Henry Spencer

Henry Spencer

William Sette

William Sette

Myron Ottly<sup>e</sup>

Myron Ottly

James Rowe

James N. Rowe

Esther Rinde

Esther Rinde

George Ghali

G. Ghali

Rick Whiting

Rick Whiting

2. Scientific Reviewer (Committee or non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report).

Robert Fricke

Robert F. Fricke

Jess Rowland

Jess Rowland

3. Others:

Flora Chow, Debbie McCall, Linnea Hansen and Alberto Protzel as observers

CC: Penny Fenner-Crisp  
Richard Schmitt  
Kerry Dearfield  
Marcia Van Gemert  
Jess Rowland  
Robert Fricke  
Rick Whiting/RfD Files  
James Kariya  
Marion Copley

## B. Material Reviewed

Material available for review included data evaluation records for a chronic toxicity/carcinogenicity study in rats (83-5 or 83-1a and -2a), a long-term toxicity study in dogs (83-1b), a carcinogenicity study in mice (83-2b), developmental toxicity studies in rats and rabbits (83-3a and -3b) and a reproductive toxicity study in rats (83-4), and a tox. one-liner. It should be emphasized that there were two sets of data available on this chemical; one submitted by Dow Chemical Company and another by Makhteshim-Agan.

1. Crown, S. et al. (1990). Pyrinex technical: oncogenicity study in the rat. Sponsor: Makhteshim-Agan, MRID No. 42172802, HED Doc. No. 009733.

**Core Classification: Core-minimum data.**

### Committee's Conclusions and Recommendations:

The chemical was tested in rats at 0.2, 5.0 and 100 ppm (equivalent to approximately 0.0132, 0.33 and 6.99 mg/kg/day for males and 0.0146, 0.365 and 7.78 mg/kg/day for females, respectively). The systemic NOEL/LOEL were determined to be 5.0 and 100 ppm in both males and females. The NOEL/LOEL for cholinesterase inhibition were determined to be 0.2 and 5.0 ppm in males and <0.2 and 0.2 ppm in females. The chemical did not alter the spontaneous tumor profile in this strain of rats. The Committee generally agreed with the reviewer's evaluation and interpretation of the data. However, the Committee revised the cholinesterase NOEL/LOEL for females to be 0.2 and 5.0 ppm. The carcinogenicity phase of the study was considered adequate, the dose levels tested were considered appropriate for carcinogenicity testing based on plasma, erythrocyte and brain cholinesterase depression. The Committee recommended that a summary table for the most frequently observed tumors be included in the data evaluation record of this study to support the conclusion made with respect to the carcinogenicity phase of the study. This study satisfies data requirement 83-1a and -2a of subpart F of the Pesticide Assessment Guideline for chronic toxicity/ carcinogenicity testing in rats.

2. Young, J. T. and Grandjean, M. (1988). Chlorpyrifos: 2-Year dietary chronic toxicity/oncogenicity study in Fisher 344 rats. Sponsor: Dow Chemical Comp[any. MRID No. 40952802, HED Doc. No. 007107.

**Core Classification: Core-minimum data.**

### Committee's Conclusions and Recommendations:

The chemical was tested in rats at 0.05, 0.1, 1.0 and 10 mg/kg/day. The NOEL/LOEL for cholinesterase inhibition were determined to be

0.1 and 1.0 mg/kg/day in males and females based upon decreased plasma and brain cholinesterase activity. The chemical did not alter the spontaneous tumor profile in this strain of rats. The Committee generally agreed with the reviewer's evaluation and interpretation of the data. The carcinogenicity phase of the study was considered adequate, the dose levels tested were considered appropriate for carcinogenicity testing based on plasma, and brain cholinesterase depression. This study satisfies data requirement 83-1a and -2a of subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

3. McCollister, S. B. (1971). Results of two-year feeding study on Dow Co 179 in Beagle dogs. Sponsor: Dow Chemical Company. MRID No. 00029063, 00064933, 00146519, HED Doc. 000179, 000191, 003822, 004712.

**Core Classification: Core-minimum data.**

**Committee's Conclusions and Recommendations:**

The chemical was tested in Beagle dogs at 0.01, 0.03, 0.1, 1.0 and 3.0 mg/kg/day. The NOEL/LOEL for cholinesterase inhibition were determined to be 0.01 and 0.03 mg/kg/day in males and females based upon decreased plasma cholinesterase activity. The systemic NOEL/LOEL were considered to be 1.0 and 3.0 mg/kg/day based upon alterations in absolute and relative liver weights. This study satisfies data requirement 83-1b of subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

4. Gur, E. (1992). Pyrinex technical: oncogenicity study in the Mouse. Sponsor: Makhteshim-Agan (america). MRID No. 42534201, HED Doc No. 010193.

**Core Classification: Core-minimum data.**

**Committee's Conclusions and Recommendations:**

The chemical was tested in CD-1 mice at dietary concentration of 5, 50, 250 ppm for 78 weeks. Plasma cholinesterase activity was significantly reduced at all dose levels. Brain cholinesterase activity was reduced at only in the high-dose animals. The NOEL/LOEL for systemic toxicity were considered to be 50 and 250 ppm based on decreased body weights in males and increased incidence of non-neoplastic lesions in male and females. The chemical did not alter the spontaneous tumor profile in this strain of mice. The Committee generally agreed with the reviewer's evaluation and interpretation of the data. The dose levels tested were considered appropriate for carcinogenicity testing based on plasma, and brain cholinesterase depression and increase non-neoplastic lesions in both sexes and body weight decrease in males. This study satisfies data requirement 83-1b of subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

5. Breslin, W. J. et al. (1991). Chlorpyrifos: Two-generation dietary reproduction study in Sprague-Dawley rats. Sponsor: DowElanco Chemical Co. MRID No. 41930301, HED Doc. No. 009779.

**Core Classification: Guideline**

**Committee's Conclusions and Recommendations:**

The chemical was tested in Sprague-Dawley rats at dietary concentration of 0.1, 1.0 and 5.0 mg/kg/day for 10 or 12 weeks prior to mating (F0 or F1, respectively), with exposure continuing through lactation and weaning. Cholinesterase inhibition in plasma, red blood cells and brain was observed in parental animals of the 1.0 and 5.0 mg/kg/day groups. Histopathological changes of the adrenal glands were observed in parental animals at 5.0 mg/kg/day. The NOEL/LOEL for reproductive/developmental effects were considered to be 1.0 and 5.0 mg/kg/day respectively based upon reduced pup weights and increased mortality. Maternal/systemic toxicity NOEL/LOEL were considered to be 0.1 and 1.0 mg/kg/day based on decreased cholinesterase activity. The Committee generally agreed with the reviewer's evaluation and interpretation of the data. The dose levels tested were considered appropriate for reproductive toxicity testing. This study satisfies data requirement 83-4 of subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

6. James, P. (1989). The effect of Pyrinex (chlorpyrifos) on reproductive function of two generations in the rat. Sponsor: Makhteshim-Agan (America). MRID No. 42172803, HED Doc. No. 009733.

**Core Classification: Core-supplementary data.**

**Committee's Conclusions and Recommendations:**

The chemical was tested in Sprague-Dawley rats at dietary concentration of 2, 10 and 50 ppm (equivalent to 0.13, 0.64 and 3.21 mg/kg/day for F0 males, and 0.19, 1.03, 5.05 mg/kg/day for F1 males, 0.14, 0.71 and 3.58 mg/kg/day for F0 females, and 0.21, 1.08 and 5.44 mg/kg/day. Cholinesterase inhibition was not measured in this study. The NOEL/LOEL for reproductive/developmental effects as well as maternal/systemic toxicity NOEL/LOEL could not be determined for lack of necessary information. The Committee agreed with the reviewer's evaluation and interpretation of the data and the classification of the study. This study, as presented, does not satisfy data requirement 83-4 of subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

7. Dow Chemical Co. (1971). Three-generation reproduction study in rats. MRID No. 00029064, 00064934, HED Doc. No. 000179, 000191.

**Core Classification: Core-supplementary data.**

**Committee's Conclusions and Recommendations:**

The chemical was tested in Sprague-Dawley rats at dietary concentration of 0.1, 0.1 and 0.3. Due to the lack of basic information, the NOEL/LOEL for reproductive/developmental effects as well as maternal/systemic toxicity NOEL/LOEL could not be determined. Therefore, the Committee recommended to downgrade the study to a Core-supplementary status. This study, as presented, does not satisfy data requirement 83-4 of subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

8. Rubin, Y. et al. (1987). Pyrinex: Teratogenicity study in the rat. Sponsor: Makhteshim-Agan (America). MRID No. 40436407, HED Doc. No. 006851.

**Core Classification: Core-minimum data.**

**Committee's Conclusions and Recommendations:**

The chemical was tested in CD rats at 0.5, 2.5 and 15.0 mg/kg/day. Maternal toxicity NOEL was not determined. Plasma cholinesterase inhibition was observed at the lowest dose level. Systemic NOEL/LOEL were determined to be 2.5 and 15 mg/kg/day based upon decrease body weight gain and food consumption. Developmental toxicity NOEL/LOEL were determined to be 2.5 and 15 mg/kg/day based on post-implantation loss. The Committee agreed with the reviewer's evaluation and interpretation of the data. This study satisfies data requirement 83-3a of subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

9. Rubin, Y. et al. (1987). Pyrinex: Teratogenicity study in the rabbit. Sponsor: Makhteshim-Agan (America). MRID No. 40436408, HED Doc. No. 007302.

**Core Classification: Core-minimum data.**

**Committee's Conclusions and Recommendations:**

The chemical was tested in New Zealand HY/CR rabbits at 1.0, 9.0, 81 and 140 mg/kg/day. Maternal toxicity NOEL was not determined. Plasma cholinesterase inhibition was observed at the lowest dose level. Maternal/systemic NOEL/LOEL were determined to be 81 and 140 mg/kg/day based upon decreased food consumption during gestation days 15-19, and body weight during dosing followed by compensatory weight gain, suggestion of post-implantation loss. Developmental toxicity NOEL/LOEL were determined to be 81 and 140 mg/kg/day based upon slight reduction in fetal weights, crown-rump lengths and increased incidence of unossified 5th sternebra and/or xiphisternum. The Committee agreed with the reviewer's evaluation and interpretation of the data. This study satisfies data requirement 83-3b of subpart F of the Pesticide Assessment

Guideline for developmental toxicity testing in rabbits.

10. Dow Chemical Company (1979). Developmental Toxicity study in mice. MRID No. 00095268, HED No. 00181.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

There were no data tables associated with this data evaluation record of this study. The Committee suggested that this study should either be re-evaluated or down-graded in the tox. one-liner for this chemical. This study, as presented, does not satisfy data requirement 83-3 of subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.



## C. Conclusions and Recommendations:

### 1. Data Base

The Committee considered the chronic toxicity/carcinogenicity study in rats (83-1a and -2a), the long-term feeding study in dogs (83-1b), the carcinogenicity study in mice (83-2b), the developmental toxicity studies in rats and rabbits (83-3a and -3b) and the reproductive toxicity study in rats (83-4) to be acceptable. The Committee recommended that summary tables of the most frequently observed tumors in both the rat and mouse studies be included in the data evaluation records for these studies.

### 2. Reference Dose

The Reference Dose (RfD) has been assessed by the Health Effects Division-RfD Committee in February 1986 and verified by the Agency RfD Work Group in November 1986. The RfD was based upon a no-observable effect level (NOEL) of 0.03 mg/kg/day for plasma cholinesterase inhibition in human subjects using an Uncertainty Factor (UF) of 10 to account for the intraspecies variability. On this basis, the RfD was calculated to be 0.003 mg/kg/day. The Committee recommended that the existing Reference Dose remain unchanged. It should be noted that an RfD value of 0.01 mg/kg/day for chlorpyrifos was established by the WHO in 1982.

### 3. Carcinogenicity

The high dose levels tested in the carcinogenicity studies in rats and mice were considered adequate for carcinogenicity testing as demonstrated by the depression of cholinesterase. The chemical did not alter the spontaneous tumor profile in these strains of rats and mice under the testing conditions. The chemical was, therefore, classified as a "Group E" carcinogen.

### 4. Other Toxic Effects

Since chlorpyrifos is a potent cholinesterase inhibitor and has the potential to cause other neurotoxic effects, the Committee determined that developmental as well as subchronic neurotoxicity studies should be conducted. The Committee felt that ocular effects should be addressed.